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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,482	09/23/2003	**Claudio Cavazza**	4865-62	9079

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EXAMINER	
KIM, JENNIFER M	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
05/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,482	CAVAZZA, CLAUDIO	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *May 2, 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14,17-22 and 25-35* is/are pending in the application.

4a) Of the above claim(s) *17-22,25-30 and 33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 2, 2008 has been entered.

It is noted that claims 12-14, 31 and 32 are being examined only to the extent of Applicants' elected species of lithium as a nephrotoxic or potential nephrotoxic external agent and claims 17-22, 25-30 and 33-35 are withdrawn from consideration since they are non-elected invention.

Action Summary

The rejection of claims 9-11 under 35 U.S.C. 112, first paragraph (enablement) is being expressly **withdrawn** in view of Applicant's amendment.

The rejection of claims 31 and 32 under 35 U.S.C. 112, first paragraph (New Matter) is being expressly **withdrawn** in view of Applicant's amendment.

The rejection of claims 31 and 32 under 35 U.S.C. 112, second paragraph is being expressly **withdrawn** in view of Applicant's amendment.

The rejection of claims 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calvani et al. (U.S. Patent No. 5,955,424) is being **maintained** for the reasons stated in the previous Office Action. However, the rejection is modified in this Office Action to exclude canceled claims.

The rejection of claims 9-16, 23-24, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calvani et al. (U.S. Patent No. 5,955,424) in view of Walker et al. (1982) being **maintained** for the reasons stated in the previous Office Action. However, the rejection is modified in this Office Action to exclude canceled claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calvani et al. (U.S. Patent No. 5,955,424) of record.

Calvani et al. teach the pharmaceutical composition comprising L-carnitine or an alkanoyl L-carnitine or a pharmacologically acceptable salts thereof, useful as a medicament for inhibiting nephrotoxicity resulting from the administration of an immunosuppressant drug such as cyclosporine-A, tacrolimus, rapamycin and deoxyspergualine. (abstract). Calvani et al. illustrate tests showing carnitine-induced renal protection with administration of **acetyl L-carnitine** or **propionyl L-carnitine**. (see Experimental tests, column 3-6). Calvani et al. teach the effective amount of L-carnitine in two different doses of 2mg/l and 5mg/l.

Calvani et al. do not expressly teach the composition comprising acetyl L-carnitine and propionyl L-carnitine in a single formulation for inhibiting nephrotoxicity.

It would have been obvious to one of ordinary skill in the art to combine acetyl L-carnitine and propionyl L-carnitine in a single formulation for inhibiting nephrotoxicity because Calvani et al. teach that each of the active agents are effective for the such inhibition. One of ordinary skill in the art would have been motivated to combine acetyl L-carnitine and propionyl L-carnitine in a single formulation in order to achieve an expected additive benefit of inhibiting nephrotoxicity as illustrated by Calvani et al. One of ordinary skill in the art would have been reasonably expect that the obvious method

would provide kidney protection from a kidney dysfunction/nephropathy caused by nephrotoxic agent (cyclosporine, tacrolimus, rapamycin) because each of the active agents has a renal protective effect as demonstrated by Calvani et al.

Claims 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calvani et al. (U.S. Patent No. 5,955,424) of record in view of Walker et al. (1982).

Calvani et al. teach the pharmaceutical composition comprising L-carnitine or an alkanoyl L-carnitine or a pharmacologically acceptable salts thereof, useful as a medicament for inhibiting nephrotoxicity resulting from the administration of an immunosuppressant drug such as cyclosporine-A, tacrolimus, rapamycin and deoxyspergualine. (abstract). Calvani et al. illustrate tests showing carnitine-induced renal protection with administration of **acetyl L-carnitine** or **propionyl L-carnitine**. (see Experimental tests, column 3-6). Calvani et al. teach the effective amount of L-carnitine in two different doses of 2mg/l and 5mg/l. Calvani et al. teach that **acetyl L-carnitine** or **propionyl L-carnitine** is effective for treating renal toxicity of **tubular lesion** induced by cyclosporin A. (column 4, lines 38-43).

Calvani et al. do not expressly teach providing protection from a tubular necrosis caused by Lithium comprising adminsitering a composition comprising acetyl L-carnitine and propionyl L-carnitine in a single formulation.

Walker et al. teach that lithium therapy is associated with tubular lesion as a nephrotoxicity. (abstract).

It would have been obvious to one of ordinary skill in the art to combine acetyl L-carnitine and propionyl L-carnitine in a single formulation for treating tubular lesion in nephrotoxicity caused by lithium because Calvani et al. teach that each of the active agents are effective for the nephrotoxic related tubular lesion caused by cyclosporin-A and because Walker et al. teach that lithium also causes tubular lesion as nephrotoxicity. One of ordinary skill in the art would have been motivated to combine acetyl L-carnitine and propionyl L-carnitine in a single formulation in order to achieve an expected additive benefit of inhibiting tubular lesion of nephrotoxicity due to lithium. One of ordinary skill in the art would have been reasonably expect that the obvious method would provide kidney protection from a kidney dysfunction/nephropathy caused by nephrotoxic agent (lithium) because each of the active agents has a renal protective effect of treating the same nephrotoxic condition e.g. tubular lesion caused by cyclosporine-A. There is a reasonable expectation of successfully treating nephrotoxicity caused by lithium, i.e. tubular lesion because Calvani et al. specifically teaches that the each of active agents are useful for treating tubular lesion that is specific condition of nephrotoxicity.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Response to Arguments

Applicant arguments filed May 2, 2008 have been fully considered but they are not persuasive. Applicant essentially argues that Calvani et al. doe not discloses a combination comprising the two compounds in a single formulation and more importantly Calvani et al. do not refer to lithium as a nephrotoxic agent. This is not found persuasive because As stated in In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

> It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art.

Therefore, it would have been prima facie obvious to combine acetyl L-carnitine and propionyl L-carnitine cojointly in a formulation to treat tubular lesion in nephrotoxicity. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). Further, there is a reasonable expectation of successfully treating nephrotoxicity caused by lithium, because it is well known in view of Walker et al. that lithium therapy is associated with tubular lesion of nephrotoxicity and Calvani et al. teaches that the each of the active agents are useful for treating tubular lesion specific condition of nephrotoxicity. Applicant argues that the experimental results reported in from page 7-last 5 lines to

page 9-table 3, of the specification show that the combination of acetyl L-carnitine with propionyl L-carnitine has a synergistic effect. Applicant further argues that the data in table 3, it can be easily understood that the post-lithium-infusion time is halved by the combination in comparison to the two components alone. Applicant's data have been carefully reviewed and considered. However, it is not found to be persuasive because the "evidence" of alleged synergism is not commensurate in scope with the breadth of the claims. It is well established that a showing of unexpected results generally must be commensurate in scope with the breadth of the claims sought to be patented. See, inter alia, (1) In re Greenfield, 571 F.2d 1185, 1189, 197 USPQ 227, 230 (CCPA 1978) (showing of unexpected results must be commensurate in scope with breadth of claim); (2) In re Kulling, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990) (same); and (3) In re Lindner, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972) (same). In this case, it is not clear how the dosages as claimed are correlated with the data shown in Tables 2 and 3. Therefore, it appears that the claims are not commensurate in the scope with the amounts shown in the data. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Kim/
Primary Examiner, Art Unit 1617

Jmk
May 12, 2008